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Treatment of quinine overdosage with repeated oral charcoal

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In five symptomatic patients with acute quinine poisoning the mean admission plasma concentration was 11.1 mg l^{-1}. After treatment with repeated oral charcoal 50 g 4 hourly, plasma quinine concentrations fell rapidly with a mean half-life of 8.1 ± 1.1 h (s.d.) compared with more than 24 h in a previous report in similarly poisoned patients. The visual impairment which was expected in a patient with cardiotoxicity and a plasma quinine concentration of 12.6 mg l^{-1} did not occur, but late treatment with charcoal was of no obvious benefit in another patient who was already blind. Repeated oral charcoal has been shown to increase the rate of elimination of a therapeutic dose of quinine in healthy volunteers. It appears to be the only practical means of enhancing the removal of this drug after overdosage and should reduce the risk of potentially disastrous complications.

Keywords quinine overdosage blindness repeated oral charcoal enhanced elimination

Introduction

Quinine in overdosage can cause serious complications and management is unsatisfactory. Toxicity is related to plasma quinine concentrations and the risk of blindness (which may be permanent) and cardiac arrhythmias increases as concentrations rise above 10 mg l^{-1} (Dyson *et al.*, 1985; Bateman *et al.*, 1985). Attempts have therefore been made to enhance the removal of quinine by forced acid diuresis, peritoneal dialysis, haemodialysis and charcoal haemoperfusion but all these measures are ineffective (Sabto *et al.*, 1981; Bateman *et al.*, 1985).

Repeated oral activated charcoal greatly increases the rate of elimination of drugs such as anticonvulsants, salicylate, dapsone, theophylline and digoxin taken in overdosage (Neuvonen, 1982; Editorial, 1987). This effect is not due to interference with absorption but to concentration-dependent diffusion of drug from the circulation to the gastrointestinal lumen where it is irreversibly bound by the charcoal (Levy, 1982; Boldy *et al.*, 1986). Recent studies have shown that repeated oral charcoal reduces the plasma half-life of quinine by about 50% following a therapeutic dose in healthy volunteers (Lockey & Bateman, 1989). We describe here the effects of repeated oral charcoal in five patients with quinine poisoning.

Methods

Three females aged 16, 23 and 60 years and two males aged 16 and 19 years were admitted following intentional overdosage with quinine. They all developed symptoms; clinical details are summarised in Table 1. Gastric lavage was carried out and management was otherwise symptomatic and supportive. Repeated oral charcoal was started shortly after admission in patients 2–5 but treatment delayed for 34 h in patient 1. The charcoal ('Medicoal', Lundbeck Ltd) was given in a dose of 50 g as a slurry in 200 ml of water repeated every 4 h to a total dose of 200–400 g (Table 1). In patient 5 troublesome diarrhoea developed after two doses and 'Carbomix' (Penn Pharmaceuticals Ltd) was substituted.

Table 1 Clinical details of patients with quinine overdosage treated with repeated oral activated charcoal

Patient	*Age (years) sex*	*Ingestion-admission interval (h)*	*Total charcoal dose (g)*	*Admission plasma quinine (mg l^{-1})*	*Quinine $t_{1/2}$ after charcoal (h)*
1	16F	2	400	18.4	10.0
2	16M	3.5	300	8.4	7.6
3	19M	3.5	300	7.1	8.0
4	23F	4	200	8.8	7.2
5	60F	4	300	12.6	7.6

Blood was sampled at intervals and plasma quinine was estimated fluorimetrically following extraction with toluene to avoid interference by metabolites. The coefficient of variation for the method was 11% at a plasma concentration of 10 mg l^{-1}.

Results

The mean plasma quinine concentration on admission was 11.1 mg l^{-1} (range 7.1 to 18.4 mg l^{-1}). In all patients there was a rapid fall following administration of charcoal and the initial mean plasma quinine half-life was only 8.1 ± 1.1 h (s.d.) (Table 1). The quinine half-life in patient 1 before treatment was 33 h but after charcoal was started there was a striking reduction to 10 h. In patient 5 the rapid removal of quinine was not maintained after 8 h when the brand of charcoal was changed to 'Carbomix' (Figure 1).

Patient 1 was severely intoxicated and developed a broad-complex tachycardia associated with metabolic acidosis (H^+ 50 nmol l^{-1}, [pH 7.30] HCO_3^- 15 mmol l^{-1}) and hypotension. These abnormalities responded promptly to intravenous administration of 1.26% sodium bicarbonate but her vision deteriorated with dilated unreactive pupils and rapid progression to complete blindness. There was no improvement following treatment with charcoal and she remains partially blind. Symptoms of cinchonism were mild and transient in patients 2, 3 and 4. Patient 5 had more marked tinnitus and deafness, and an electrocardiogram showed prolongation of the PR, QT and QRS intervals. Visual impairment was anticipated but was not detected on repeated testing.

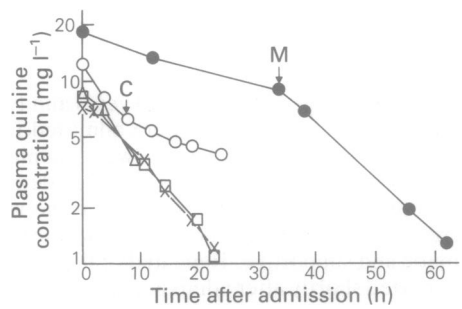

Figure 1 Plasma quinine concentrations in five poisoned patients given repeated oral activated charcoal every 4 h. Treatment with 'Medicoal' was started on admission in patients 2–5. M—Charcoal commenced in patient 1, C—'Carbomix' substituted for 'Medicoal' in patient 5. • patient 1, x patient 2, □ patient 3, △ patient 4 and ○ patient 5.

Discussion

The results of this study suggest that repeated oral charcoal is as effective in enhancing the removal of quinine in poisoned patients as it is in healthy volunteers taking a therapeutic dose (Lockey & Bateman, 1989). After treatment with charcoal, plasma quinine concentrations fell rapidly in all patients with an initial mean half-life of 8.1 h compared with the previously reported half-life of more than 24 h in 13 similarly poisoned patients (Bateman *et al.*, 1985). In another study of 48 poisoned patients (Dyson *et al.*, 1985) the rate of quinine elimination was clearly much slower than that observed in our patients after treatment with charcoal. It is possible that the metabolism of quinine is dose- or time-dependent under certain circumstances since the half-life was about 8 h in healthy subjects given a single therapeutic dose (Lockey & Bateman, 1989) and 16 h in patients with malaria (White *et al.*, 1982). However, such an effect could not fully account for the present findings.

Treatment was considerably delayed in patient 1 but the subsequent reduction in quinine half-life from 33 to 10 h is very convincing. The rate of removal of quinine de-

creased in patient 5 when 'Carbomix' was substituted for 'Medicoal' and we have seen this happen with other drugs. 'Medicoal' contains polyvinylpyrrolidone as a non-absorbable suspending agent and it often causes diarrhoea. Its greater efficacy is probably due to stimulation of gastrointestinal transit (Boldy *et al.*, 1986).

It is not possible to say whether treatment with charcoal influenced the outcome in these patients. Intoxication was not severe in patients 2, 3 and 4, and symptoms of cinchonism (including blurred vision and dilated, poorly reacting pupils) disappeared rapidly as they might have done anyway. However, on admission patient 5 had plasma quinine concentrations in the range associated with cardiac arrhythmias and blindness. There was transient cardiotoxicity but the expected visual impairment did not materialise. Unfortunately, patient 1 was already blind when treatment with charcoal was started and there was no obvious benefit. The onset of blindness after quinine overdosage is delayed for about 12 h and in retrospect the permanent deficit in this patient might have been prevented by early treatment.

The present limited study can be criticised because of the lack of controls. However, severe quinine poisoning is rare and it would take many years to obtain sufficient patients for a controlled study. More importantly, the apparent efficacy of repeated oral charcoal raises serious ethical problems in withholding treatment for a condition which can cause permanent blindness and fatal cardiotoxicity and for which there is no other effective method for drug removal.

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